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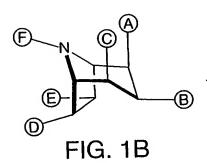
Our Ref. No. 5673-66690

For: HAPTEN-CARRIER CONJUGATES FOR USE IN DRUG-ABUSE THERAPY AND METHODS FOR PREPARATION OF SAME 121 SW Salmon Street, Suite 1600

Portland, Oregon 97204

Telephone: 503/226-7391 Express Mail Label EV339203081, mailed: August 22, 2003

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William D. Noonan, M.D.

Klarquist Sparkman, LLP

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AND METHODS FOR PREPARATION OF SAME

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Variables

CJ#	Branch	Variables
ωo	Q	Q = H, OH, CH₂, HALOGEN, COOH, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 1	(CH <sub>2</sub> ) <sub>n</sub> Q	Q = H, COOH, HALOGEN, 2-NITRO-4-SULFOPHENYL ESTER, N-OXYSUCCINIMIDYL ESTER, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN, CJ 1.2
CJ 1.1	CO <sub>2</sub> Q	$Q = H, CH_3$
CJ 1.2	COQ	Q = H, HALOGEN, 1-OXY-2-NITRO-4-SULFOPHENYL, N-OXYSUCCINIMIDYL, N-MALEIMIDYL, CARRIER PROTEIN, CJ 10
CJ 2	OCO(CH <sub>2</sub> ) <sub>n</sub> Q	Q = COOH, HALOGEN, 2-NITRO-4-SULFOPHENYL ESTER, N-OXYSUCCINIMIDYL ESTER, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 2.1	OCOCH=Q	Q = H
CJ 2.2	OCOCH(O)CH₂	
CJ 2.3	OCO(CH <sub>2</sub> ) <sub>n</sub> CH(O)CH <sub>2</sub>	
CJ 3	CO(CH₂),COQ	Q = H, $OH$ , $HALOGEN$ , $1-OXY-2-NITRO-4-SULFOPHENYL$ , $N-OXYSUCCINIMIDYL$ , $N-MALEIMIDYL$ , $CARRIER PROTEIN$ , $CJ$ 10
CJ 3.1	CO(CH <sub>2</sub> ) <sub>n</sub> CNQ	$Q = OCH_3$ or CARRIER PROTEIN
CJ 4	OCO(CH₂),COQ	Q = H, OH, HALOGEN, 1-OXY-2-NITRO-4- SULFOPHENYL, N-OXYSUCCINIMIDYL, N-MALEIMIDYL, CARRIER PROTEIN, CJ 10
CJ 4.1	CO(CH <sub>2</sub> ) <sub>a</sub> CNQ	Q = OCH <sub>3</sub> or CARRIER PROTEIN
CJ 5	CH₂OCO(CH₂)"COQ	Q = H, OH, HALOGEN, 1-OXY-2-NITRO-4- SULFOPHENYL, N-OXYSUCCINIMIDYL, N-MALEIMIDYL, CARRIER PROTEIN, CJ 10
CJ 5.1	CO(CH <sub>2</sub> ) <sub>n</sub> CNQ	Q = OCH <sub>3</sub> or CARRIER PROTEIN
CJ 6	CONH(CH <sub>2</sub> ),,Q	Q = H, COOH, HALOGEN, 2-NITRO-4-SULFOPHENYL ESTER, N-OXYSUCCINIMIDYL ESTER, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 7	Y(CH₂) <sub>n</sub> Q	Y = S, O, NH; $Q = HALOGEN$ , COOH, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 7.1	CH <sub>2</sub> Y(CH <sub>2</sub> ) <sub>n</sub> Q	Y = S, O, NH; Q = HALOGEN, COOH, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 8	OCOCH(OH)CH₂Q	Q = CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 8.1	OCO(CH <sub>2</sub> ),CH(OH)CH <sub>2</sub> Q	Q = CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 9	OCOC <sub>6</sub> H <sub>5</sub>	
CJ 11	YCO(CH <sub>2</sub> ),COQ	Y = S, O, NH; $Q = OH$ , CARRIER PROTEIN, MODIFIED CARRIER PROTEIN or HALOGEN

FIG. 2A

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## ALTERNATIVE REPRESENTATION FOR SELECTED BRANCHES

$$-\text{CON(C)OCH}_2\text{CHO'} \equiv \begin{array}{c} O \\ C)O \end{array} \qquad \begin{array}{c} \text{(WHEREIN Q' IS A MODIFIED PROTEIN)} \\ \text{CJ10} \qquad CJ10 \end{array}$$

$$-\text{OCOCH(O)CH}_2 \equiv \begin{array}{c} O \\ O \\ CJ2.2 \end{array} \qquad \begin{array}{c} O \\ CJ2.2 \end{array}$$

$$-\text{OCO(CH}_2)_n\text{CH(O)CH}_2 \equiv \begin{array}{c} O \\ O \\ CJ2.3 \end{array} \qquad \begin{array}{c} O \\ CJ2.3 \end{array}$$

$$-\text{OCOC}_6\text{H}_5 \qquad \begin{array}{c} O \\ O \\ CJ9 \end{array}$$

FIG. 2B

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	BRANCHES	HES			ш	LL
	4	В	<b>ပ</b>			
PS-2	2.1.2 1.1.2	CJ2 WHERE Q= HALOGEN OR MODIFIED T CELL EPITOPE CONTAINING	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
PS-3	CJ1.1 WHERE	CARRIER AND 11-1 CJO WHERE Q= MODIFIED T CELL EPITOPE CONTAINING	CJO WHERE Q=H	CJ0 WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
PS-4		CJ4 WHERE Q= MODIFIED T CELL EPITOPE CONTAINING	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
PS-5		CARRIEH AND N=1 CJ9	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ3 WHERE Q=CARRIER PROTEIN, n=2
PS-6		6PO	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
18		673	CJO WHERE	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
5 5		CJ2 WHERE	CJO WHERE	CJO WHERE	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
PS-10		CJ2/	CJO WHERE	CJO WHERE		CJ1 WHERE
PS-11	WHERE Q=CH <sub>3</sub>	T CELL EPITOPE CONTAINING CARRIER	표	H-0		
P.S.	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH <sub>3</sub>	CJ2.1	CJO WHERE Q=H	CJO WHERE	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
	PRECUSORS/CONJUGATES		FIG. 3B(1)			

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															_	
	CJ1 WHERE Q=H, n=1	CJ1 WHERE Q=H, n=1	O 13 WHERE	Q=H, n=1	CJ1 WHERE Q=H, n=1	אירונטנו	Q=H, n=1	CJ1 WHERE	O=H, D=1		CJ1 WHERE Q=H, n=1	C.I. WHERE	O=H, n=1	<u>9</u>	563	
	CJO WHERE Q=H	CJO WHERE Q=H	+-	CJO WHENE Q=H	CJO WHERE Q=H	L C	CJO WHERE Q=H	CJO WHERE	H=Q		CJO WHERE Q=H	ם מאוחנים ט	OSO WATER	O WHERE	H=0	
	CJO WHERE. Q=H	CJO WHERE Q=H		CJO WHERE Q=H	CJO WHERE Q=H		CJO WHERE Q=H	C.IO WHERE	H=O		CJO WHERE Q=H		CJO WHERE O=H	10 Ti 1141 Oi O	CJO WHENE Q=H	
	CJO WHERE Q=H	CJO WHERE		CJO WHERE Q=H	CJO WHERE Q=H		CJO WHERE Q=H	חמחואי סי ס	250 H=Q		CJO WHERE Q=H		CJO WHERE Q=H		CJO WHERE Q=H	
	<u>u</u>	CAHRIER AND 11=2 CJ2.2		CJ8	CJ2.3		CJ8.1		CJ4		CL 1 WHERE HALOGEN, 2 SULFOPHENY OXYSUCCINIM CARRIER PF	MODIFIED CARMIEM	CJ7		ൊ	
BRANCHES	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH <sub>2</sub>	CJ6 WHERE	WHERE Q=CH <sub>3</sub>	CJ6 WHERE Q=H OR CJ1.1	CJ6 WHERE O=H OR CJ1.1	WHERE Q=CH <sub>3</sub>	CJ6 WHERE Q=H OR CJ1.1	WHERE Q=CH <sub>3</sub>	CJ6 WHERE Q=H OR CJ1.1	WHERE C=Cn3	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH <sub>3</sub>		CJ6 WHERE Q=H OR CJ1.1	WHERE Q=CH <sub>3</sub>	OJ6 WHERE O=H OR CJ1.1	WTETT 615.3
	PS-13		<u>+</u>	PS-15	0.7		DS.17		PS-18		PS-19		PS-20		PS-21	

PRECUSORS/CONJUGATES

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			BRANCHES		<u> </u>		
Lă	PS-22	HS 문문	CJ9	CJO WHERE	CJO WHERE	CJO WHERE O	CJ1 WHENE Q=CJ 1.2
		WHERE Q=CH <sub>3</sub>	<u>a</u>	CJO WHERE	CJO WHERE	CJO WHERE	CJ1 WHERE
<u>a                                    </u>	PS-23	c CO		CJO WHERE	CJO WHERE	CJO WHERE	CJ1 WHERE
۵.	PS-24	CJ7.1	873	C=D	O WHERE	CJ0 WHERE	CJ1 WHERE
<u>α</u>	PS-25	CJ2	സ			H=Q	H=O
<u>- ۱</u> ۰	96.29	5.11.2	ero	CJO WHERE	CJO WHERE	CJO WHERE	CJ1 WHENE
		CJ6 WHERE Q=H OR CJ1.1	CJ9	CJ2	CJO WHERE	CJO WHERE	CJ1 WHERE Q=H, n=1
	_	WHERE Q=CH <sub>3</sub>					
<u> </u>	PS-28	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH <sub>3</sub>	CJ9	OCL1 WHERE CONTAINSING CARRIER, MODI- FIED T CELL EP- ING CARRIER CONTAIN- ING CARRIER CONTAIN- ING CARRIER CONTAIN- ING CARRIER CONTAIN-	CJO WHERE	CJO WHERE	CU1 WHERE Q=H, n=1
					1	ט וס אירובם ב	
<u> </u>	PS-29	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH3	CJ9	CJ2.2	CJO WHENE Q=H	HEO OSO	
	PS-30	CJ6 WHERE Q=H OR CJ1.1	6°C	CJ8	CJO WHERE	CJO WHERE	CJ1 WHERE Q=H, n=1
	PS-31		CJ9	CJ2.3	CJO WHERE	CJO WHERE	CJ1 WHERE Q=H, n=1
	ECUS	PRECUSORS/CONJUGATES		FIG. 3B(3)			

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BRANCHES CJ6 WHERE		뾔	1	9	CJO WHERE	CJO WHERE	CJ1 WHERE
PS-32 Q=H OR CJ1.1 CJ9 WHERE Q=CH <sub>3</sub>		സ		CJ8.1		H=0	0=H, n=
PS-33 Q=H OR CJ1.1 CJ9 WHERE Q=CH <sub>3</sub>		സ്ത		CJ4	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHENE Q=H, n=1
CJ6 WHERE PS-34 Q=H OR CJ1.1 CJ9 WHERE Q=CH2		CJ9		CJS	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
CJ6 WHERE PS-35 Q=H OR CJ1.1 CJ9		CJ9		CJO WHERE Q=H	CJ2	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
PS-36 WHERE Q=CH <sub>3</sub>	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH <sub>3</sub>	CJ9		CJO WHERE Q=H	CL1 WHERE Q= COOH, HALOGEN 2-NITRO-4- SULFOPHENYL ESTER, N-OXY- SUCCINIMIDYL ESTER, CARRIER PROTEIN, MODI- FIED T CELL EP- ITOPE CONTAIN- ING CARRIER, CJ1.2	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
PS-37 Q=H OR CL1.1 CJ9	CJ6 WHERE Q=H OR CL1.1	6FO		CJO WHERE Q=H	CJ2.2	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
	WHERE CECH3 CJ6 WHERE Q=H OR CL1.1	റോ		CJO WHERE Q=H	CJ8	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
PS-39 WHERE CI-CUS WHERE CJ9 CJ9 WHERE CI-CUS WHERE CJ9	WHERE GECHS CJ6 WHERE Q=H OR CL1.1 WHERE O=CH			CJO WHERE Q=H	CJ2.3	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
PRECUSORS/CONJUGATES	ORS/CONJUGATES	S	i i	FIG. 3B(4)	(4)		

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	SHONVAR	SH				
PS-40	CJ6 WHERE O=H OR CJ1.1	6PO	CJO WHERE Q=H	CJ8.1	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
	WHERE CECH <sub>3</sub> CJ6 WHERE	673	CJO WHERE	CJ4	CJ0 WHERE Q=H	CJ1 WHERE Q=H, n=1
ך 4	WHERE Q=CH <sub>3</sub>		5			O 13 WHERE
PS-42	CJ6 WHERE Q=H OR CJ1.1	600	CJO WHERE Q=H	CJS	C30 WHENE Q=H	Q=H, n=1
	WHERE CEORS					א אירוסם
PS-43	CJ6 WHERE Q=H OR CJ1.1	6PO	CJO WHERE Q=H	CJO WHERE Q=H	CJ2	O=H, n=1
	WHERE CECES				CI 1 WHERE Q=	
PS-44	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH <sub>3</sub>	ලෙට	CJO WHERE Q=H	CJO WHERE Q=H	COOH, HALOGEN 2-NITRO-4- SULFOPHENYL ESTER, N-OXY- SUCCINIMIDYL ESTER, CARRIER PROTEIN, MODI- FIED T CELL EP- ITOPE CONTAIN- ING CARRIER, CARRIER, CARRIER, CONTAIN-	CJ1 WHERE Q=H, n=1
PRECUS	PRECUSORS/CONJUGATES	<b>(</b> 0				

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	SHONVOO	SH T				
DC.45	CJ6 WHE Q=H OR C	CJ9	CJO WHERE Q=H	CJO WHERE Q=H	CJ2.2	CJ1 WHERE Q=H, n=1
} > -						O 13 WHERE
PS-46	CJ6 WHERE Q=H OR CJ1.1	CJ9	CJO WHERE Q=H	CJO WHERE Q=H	CJ8	Q=H, n=1
) 						C 13 WHERE
PS-47	CJ6 WHERE Q=H OR CJ1.1	6PO	CJO WHERE Q=H	CJO WHERE Q=H	CJ2.3	O=H, n=1
: ) 						C.11 WHERE
DC. 48	1	6°C)	CJO WHERE Q=H	CJO WHERE Q=H	CJ8.1	Q=H, n=1
} -						C.11 WHERE
06.40	CJ6 WHERE O=H OR CJ1.1	6FO	CJO WHERE Q=H	CJO WHERE Q=H	CJ4	Q=H, n=1
ř SL						C 1 WHEBE
P.S50	CJ6 WHERE Q=H OR CJ1.1	6FO	CJO WHERE Q=H	CJO WHERE Q=H	CJS	Q=H, n=1
) - -	WHERE Q=CH <sub>3</sub>					
PRECU	PRECUSORS/CONJUGATES	S				
			FIG 38(6)	(5		

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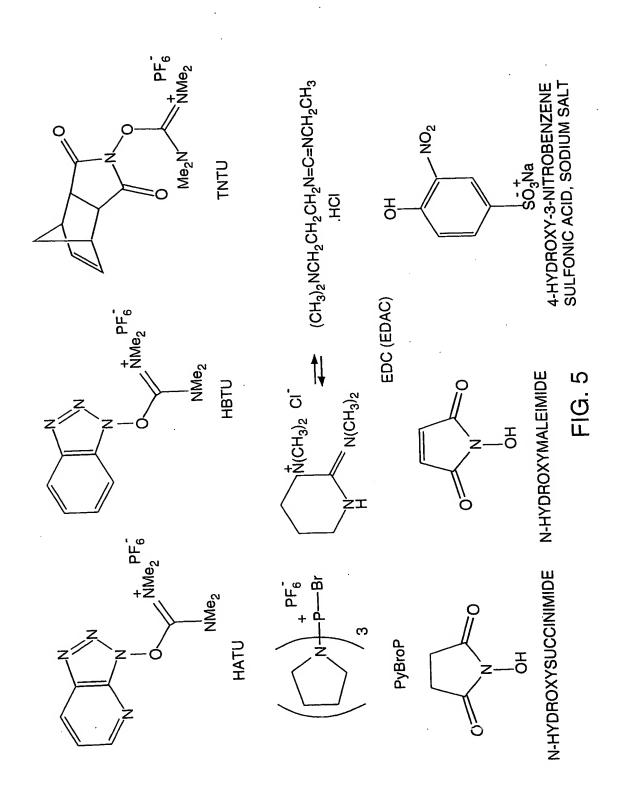
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		a	C	_	ц	
	A	2			7071 1100	אותבטע די ט
COCAINE	CJ1.1	വേ	뀖	CJO WHERE CJO WHERE	CJO WHERE	O=H. n=1
	WHERE		I J	ا ا	i y	
	Q=CH3				בים ביות היים כי כי	AGRUM TO
ECOGONINE	S1.1	CJ10 WHERE CJ0 WHERE	CJ0 WHERE	CJO WHERE	CJU WHENE Q=H	Q=H, n=1
METHYL	WHERE	C=D	ב ט	- [	,	
ESTER	C=CH3				חסיוטאי טי ט	C IO WHERE
NORCOCAINE	CJ1.1	673	CJO WHERE	CJO WHENE	H=0	H=O
	WHERE		I J	ב ש	i j	
	Q=CH3				ממחווא מי ט	C I WHERE
BENZOYI	വാ	ഗോ	CJO WHERE	CJO WHERE	0.00 WEENE	O=H, n=1
FCGONINE	WHERE		Į J	ב ש	; }	
) )	D=COOH					

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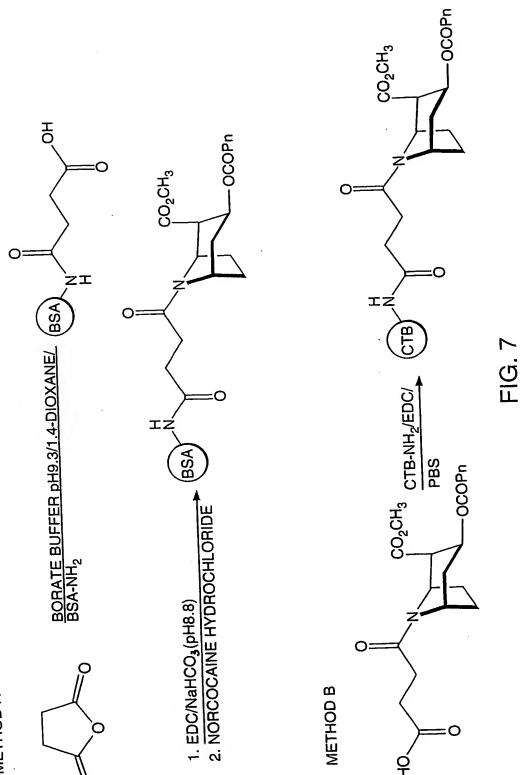
## OTHER COMMONLY ABUSED DRUGS

**AMPHETAMINE** 

**NICOTINE** 

FIG. 6

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METHOD A

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WHERE Q = CI, 
$$NO_2$$
  $NO_2$   $NO_3$   $NO_3$ 

FIG. 8

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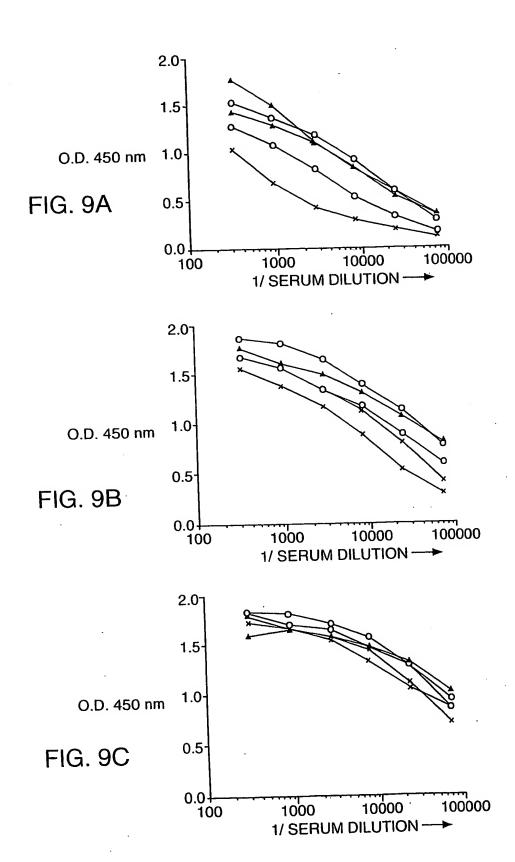
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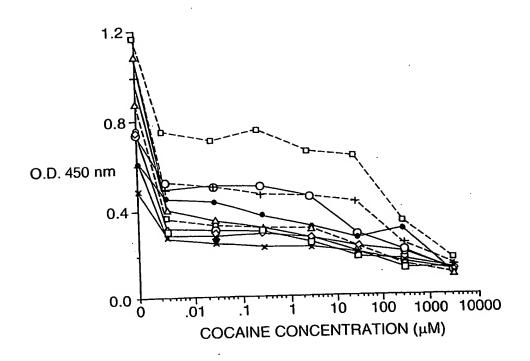


FIG. 10A

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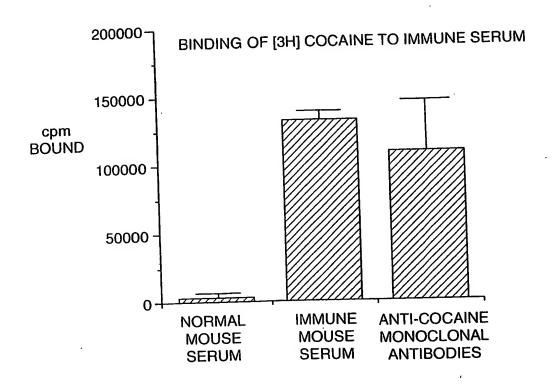


FIG. 10B

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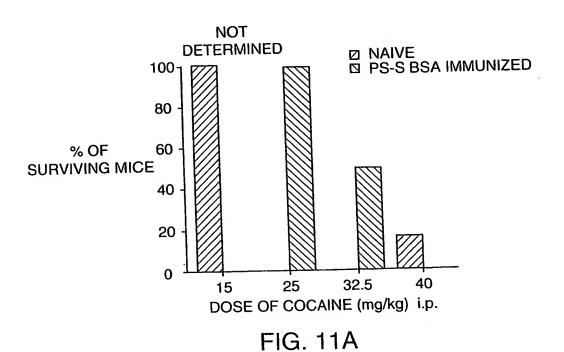
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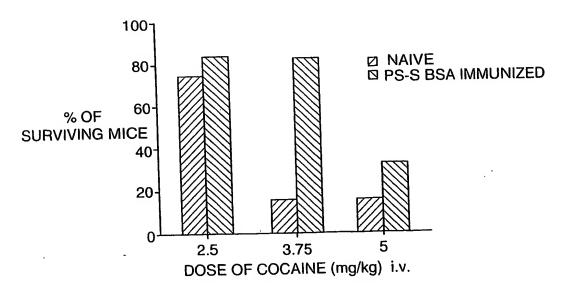


FIG. 11B

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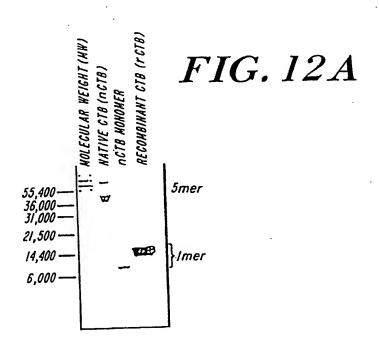
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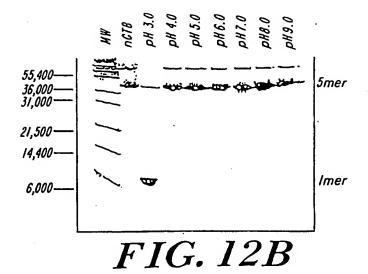
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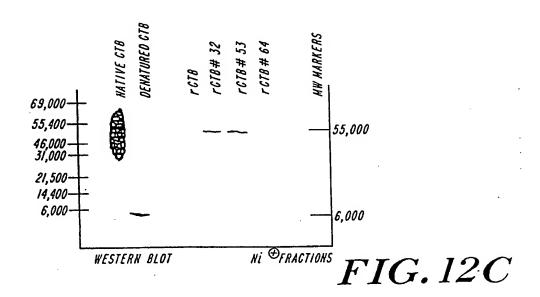
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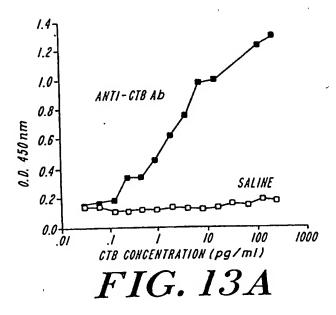
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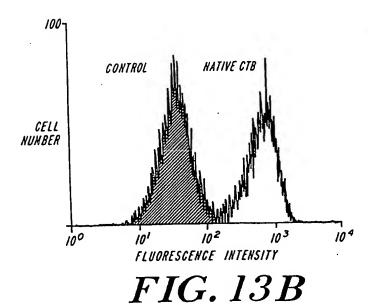
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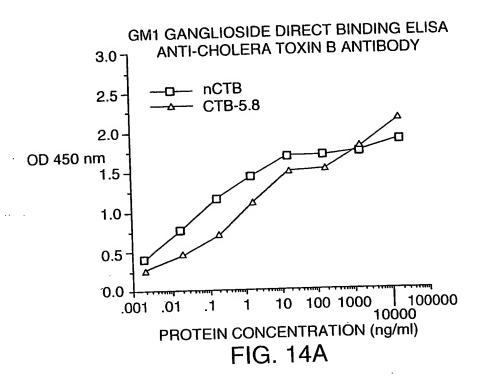
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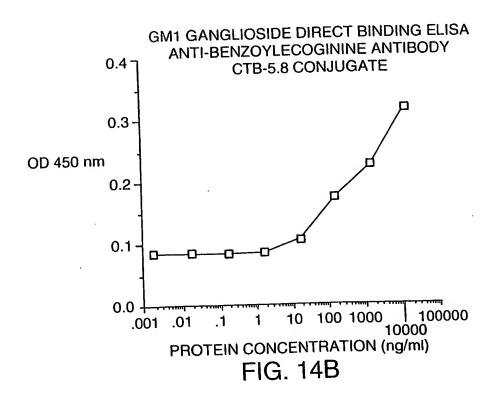
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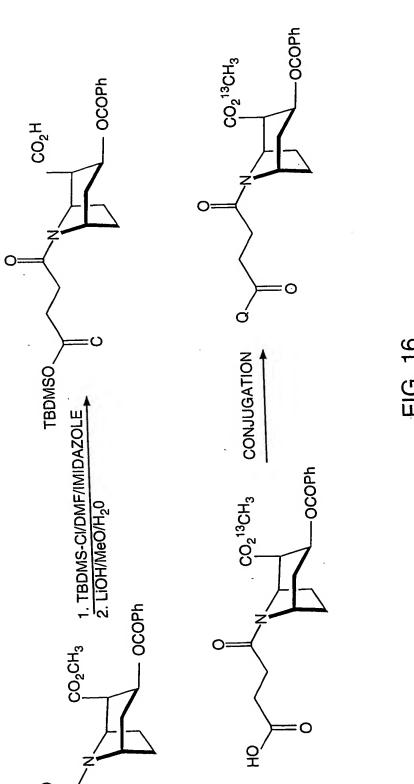
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FIG. 15

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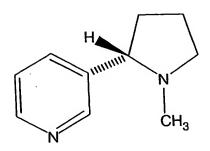


FIG. 17A

FIG. 17B

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	_	Ex	press	Mail Label E	V339203081, ma	iled	August 22	2, 2003 ^- <sub>1</sub>	Sheet 27 of 37	· <del>/</del>
F	CJ0 where Q=CH <sub>3</sub>		CJ0 where Q=CH <sub>3</sub>		CJ0 where Q=CH <sub>3</sub>	CJ3 where Q=OH or	T-cell epitope containing carrier, n=2	CJ0 where Q=CH <sub>3</sub>	CJ0 where Q=CH <sub>3</sub>	CJ0 where Q=CH <sub>3</sub>
ч								CJ1 where Q=H or a T-cell epitope containing carrier n=3	CJI where Q=H or a T-cell epitope containing carrier n=4	CJ1 where Q=H or a T-cell epitope containing carrier n=5
		CJO where Q=n	CIO where O=H		CJO where Q=H		CJO wnere u=n	CJO where Q=H	CJO where Q=H	CJO where Q=H
	٠	CJO where Q=H	U - O cred 010	CO where can	CJ1 where $Q=COOH$ or where $Q=CJ1.2$ , wherein $Q=T-cell$ epitope containing	carrier.	CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H
	В	CJO where Q=H	1,000	CJI where Q=CUOH or where Q=CJ1.2, wherein Q=T-cell epitope containing	CJO where Q=H		CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H
	4	CJ1 where Q=COOH or where Q=CJ1.2, wherein Q=T-cell epitope containing	carrier.	CJO where Q=H	CJO where Q=H		CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H
		PS-51		PS-52	PS-53		PS-54	PS-55	PS-56	PS-57

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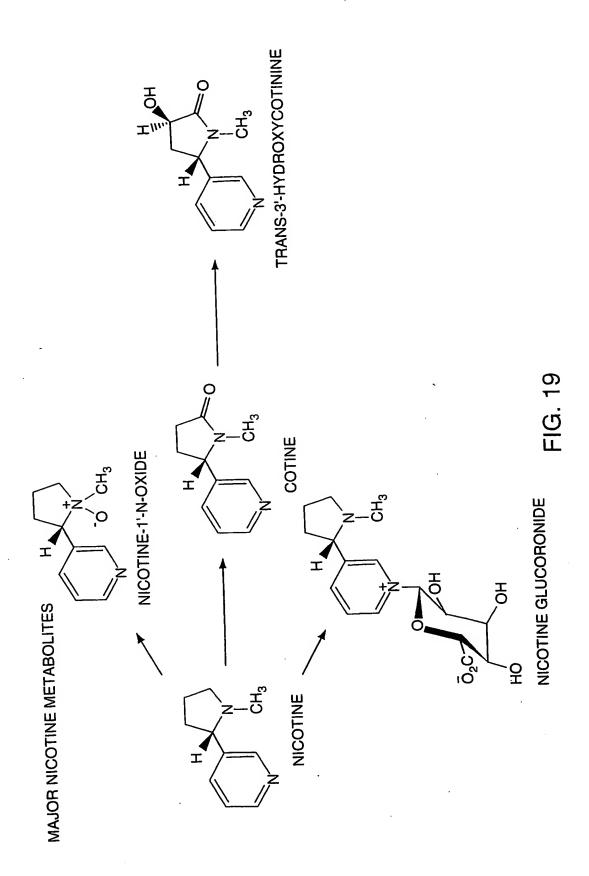
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				_ Ē	хрге	ss N	/ail	Lal	bel E	V339	2030
u		CJ0 where Q=CH <sub>3</sub>		CJ0 where Q=CH <sub>3</sub>				CJ0 where Q=CH <sub>3</sub>			
1	2	C.11 where Q=H or a	7-cell epitope containing carrier n=7	-				:			
	a	CIO where D=H		H-O ampara O-H				H-O ambara OLA			
	U	11 - O - 11 - O - O	CJO where $\alpha = n$		CJO where v=n			17 0	CJO wnere ⊄=⊓		-
	ď		CJO where Q=H		CJO where Q=H				CJ11 where Y=NH	epitope containing	carrier
		¥	CJO where Q=H		CJ11 where Y=NH	0=0H or T-cell	epitope containing	carrier	CJO where Q=H		
			PS-58		PS-59				PS-40		-

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FIG. 20

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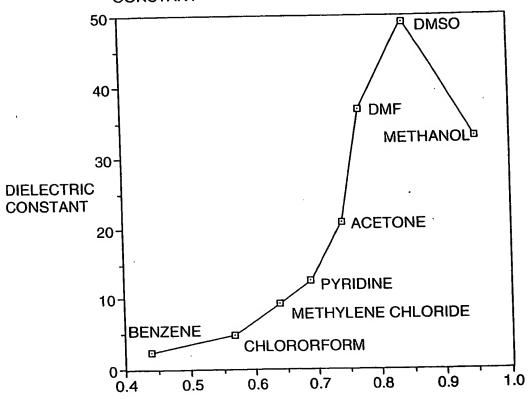
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#### RATIO OF SUCCINYLATED NORCOCAINE ISOMERS AS A FUNCTION OF SOLVENT DIELECTRIC CONSTANT



RATIO OF TWO ISOMERIC FORMS

FIG. 21

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DISTANCE TOO FAR BETWEEN ESTER AND NITROGEN FOR ENHANCED STABILITY OF INTERMEDIATE **PSEUDOCOCAINE** OMe 0 0 OMe 오 NON-STABLILIZING GROUP INTERMEDIATE OF COCAINE HYDROLYSIS 0 오 OMe 

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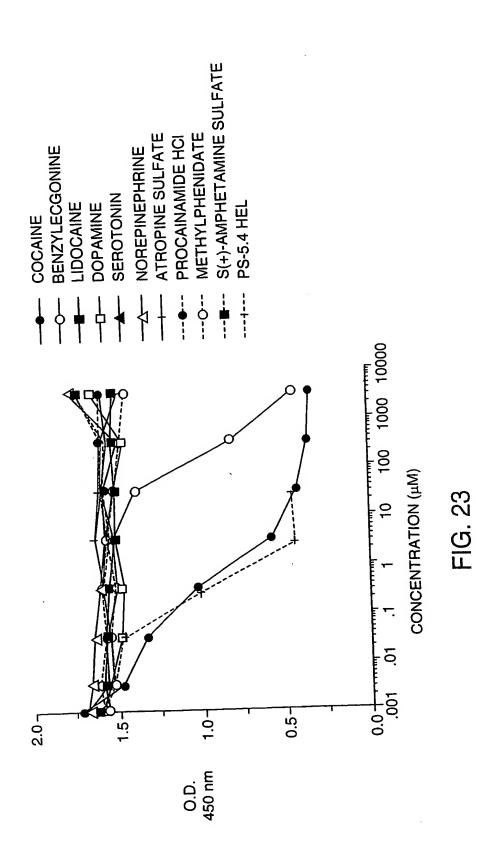
HYDROLYZED SUCCINYLATED NORCOCAINE INTERMEDIATE

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### STRONG ANTIBODY RESPONSES INDUCE BY NICOTINE-BSA CONJUGATE

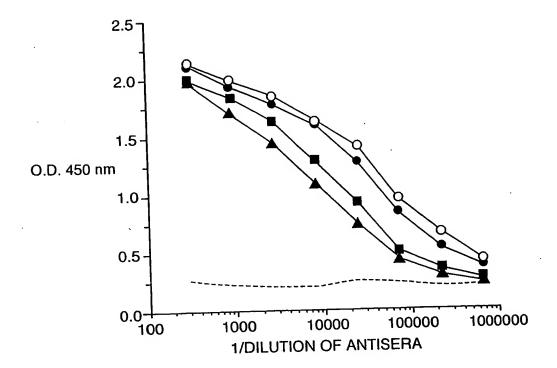


FIG. 24

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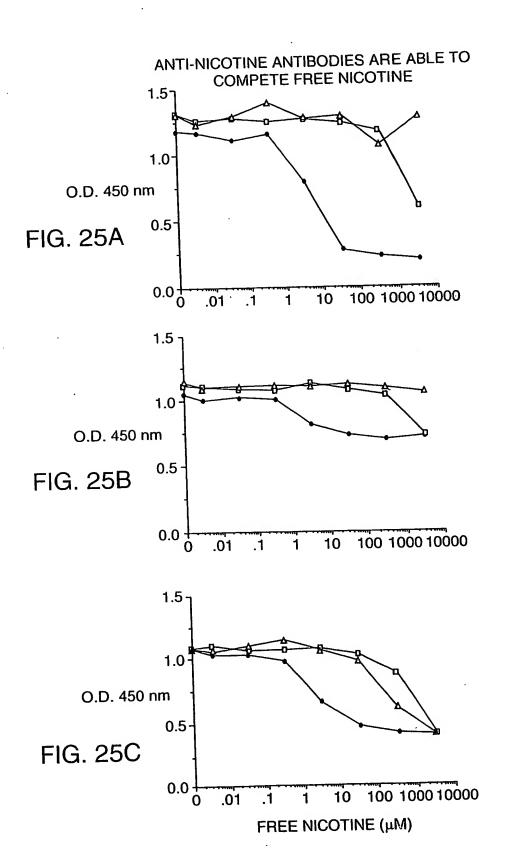
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#### Production of anti-cocaine antibodies in Wistar rats

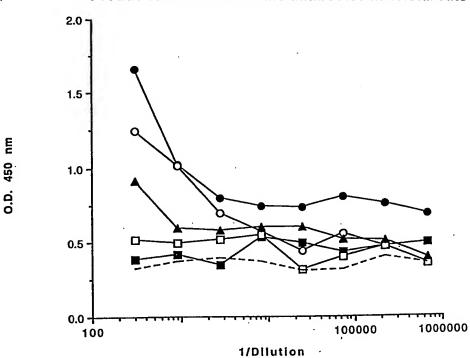


FIG.26

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### ANTI-COCAINE ANTIBODIES GENERATED IN WISTAR RATS ARE ABLE TO BIND FREE COCAINE

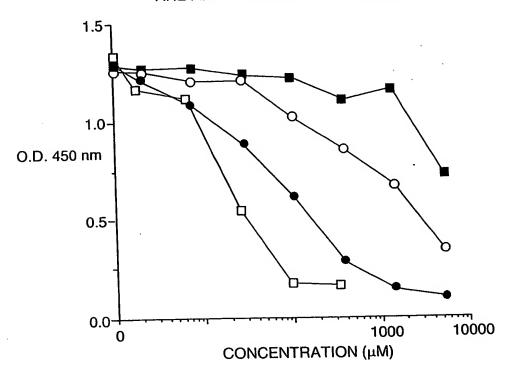


FIG. 27